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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SHAFER, SHULAMITH H	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 01/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/346,470	HILL ET AL.	
	Examiner	Art Unit	
	Shulamith H. Shafer, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *14 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *79-85 and 88-95* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *79-81 and 88-95* is/are rejected.

7)☐ Claim(s) *82-84* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 July 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims:

The Art Unit location of your application in the USPTO and the Examiner prosecuting this application has been changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Shulamith H. Shafer, Art Unit 1647.

Applicant's response to the Non-Final Office Action of 27 April 2005 and the Notice of Noncompliant Amendment of 6 October 2005 have been received on 26 September 2005 and 14 October 2005 and entered in full. Claims 79-85 and 89-95 are pending in this application. Claims 86 and 87 have been canceled at the request of the applicant. Amendments to Claims 85 and 95 received on 26 September 2005 have been entered in full. Applicant refers to Exhibit A and Exhibit B in communication received on 26 September 2005, but this Office cannot respond to information contained in these Exhibits, as they did not accompany the response of 26 September 2005.

The Applicant's arguments filed on 26 September 2005 will be responded to herein. The text of those sections of Title 35, U. S. Code not included in this action can be found in a prior Office action.

Objections

Claims:

Claim 90 is objected to because of the following informalities: Claim 90 reads "further encodes and EcR". Claim should read "further encodes an EcR". Appropriate correction is required.

Claims 82-84 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Rejections Maintained/New Grounds for Rejections

35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 79-81, 85 and 89-95 are rejected under 35 U.S.C., second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 79-81, and 90 are indefinite in reciting the term "consists essentially of" an amino acid (Claims 79, 81 and 90) or nucleotide sequence (Claim 80). This term is not defined in the specification; one of ordinary skill in the art would not be able to determine which molecules are within the scope of the claims.

Claims 91-94 are included in this rejection as being dependent on claims 79-81 and 90 and failing to resolve the indefiniteness issue.

Claims 85 and 95 are indefinite in reciting the term "substantially identical" to amino acid sequence (Claim 85) or nucleic acid (Claim 95). The specification does not define how identical a sequence must be to retain the functionality of the identified molecule.

Claims 88 and 89 are included in this rejection as being dependent on claims 85 and 95 and failing to resolve the indefiniteness issue.

35 U.S.C. § 112, First Paragraph:

Claims 79-81, 85 and 89-95 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

1. an isolated nucleic acid encoding or complementary to a sequence which encodes an ecdysteroid receptor (EcR) polypeptide that binds edysone comprising the sequence set forth in SEQ ID NO:10; or
2. an isolated nucleic acid molecule comprising the sequence set forth in SEQ ID NO:9; or
3. an isolated nucleic acid molecule of 1 or 2 wherein the nucleic acid molecule further encodes an EcR partner protein (USP polypeptide) of comprising SEQ ID NO:12; or
4. an isolated nucleic acid molecule as in 3 wherein the USP polypeptide is encoded by the nucleic acid sequence set forth in SEQ ID NO:11

does not reasonably provide enablement for

1. an isolated nucleic acid encoding or complementary to a sequence which encodes an ecdysteroid receptor (EcR) polypeptide that binds edysone consisting of an amino acid sequence consists essentially of or is substantially identical to that set forth in SEQ ID NO:10; or
2. an isolated nucleic acid wherein the isolated nucleic acid encodes an ecdysteroid receptor (EcR) polypeptide that binds edysone consisting of an amino acid sequence consisting essentially of or substantially identical to that set forth in SEQ ID NO:10 and further encodes a USP polypeptide; or a
3. an isolated nucleic acid molecule comprising a nucleic acid sequence that consists essentially of or is substantially identical to the nucleotide sequence set forth in SEQ ID NO:9 or a sequence complementary to said sequence.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

The claims are drawn to an isolated nucleic acid molecule comprising a nucleotide sequence which encodes or is complementary to a sequence consisting essentially of that set forth in SEQ ID NO:10, an isolated nucleotide sequence which further encodes an EcR partner protein (USP protein) which consists essentially of SEQ ID NO:12, the nucleic acid molecules consisting essentially of SEQ ID NOs 9 and 11 and molecules substantially identical to those identified above. SEQ ID NO:10 is identified as a sequence which encodes an edysteroid receptor that binds ecdysone.

However, the claims do not recite structural limitations for the recited receptor and partner proteins. Variants of these sequences, even if they are described as consisting essentially of or being substantially identical, are not enabled for the following reasons. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited.

Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in provident the correct three-dimensional spatial orientation of binding and activity sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). Applicant has defined the term "substantially identical" to "include any sequence which is at least about 95% identical ..... to a stated nucleotide sequence or amino acid sequence, including any homologue, analogue or derivative....." (page 22, lines 12-15). However, applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), the nature and extent of changes that can be made in these positions and the properties or characteristics of the sequences that are required for a functional protein that is identifiable as an ecdysone receptor. Applicants assert, in communication dated 26 September 2005 (page 6, 1st paragraph), that at an informal telephone interview, the previous Examiner indicated that examples of ecdysone receptors of at least 60% sequence identity to SEQ ID NO:10 would overcome the rejection. However, the contents of this interview were not made of record, and therefore applicants' statements cannot be considered. The only interview made of record took place on 27 June 2002. Examiner's notations indicate that a discussion of rejection under 102 and 112, first and second paragraph took place, but there is no written record of the decisions reached at this interview. Applicants assert that the results of sequence comparisons in which two ecdysone receptor clones from *N. virdula* show 72.9% and 73.4% sequence identity to SEQ ID NO:2 (Exhibit A) and the ecdysone receptor of *B. tabacai* shows 71.6% sequence identity to SEQ ID NO:10 (Exhibit B), but this Office cannot respond to information contained in these Exhibits, as they did not accompany the response of 26 September 2005.

Thus, the specification does not provide adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to

use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The ability of one skilled in the art to carry out site-directed mutagenesis, and test the resulting muteins for ecdysone-binding activity is not in question. However, to determine which amino acid substitutions may be made in expressed sequences in an insect where ecdysone hormones are present (either at ecdysone binding sites, or at surrounding residues) and still result in a protein retaining the required functional activity of an ecdysone receptor protein, i.e. ecdysone binding activity, would require undue experimentation.

Due to the large quantity of experimentation necessary to generate the infinite number of molecules that "consist essentially" of the disclosed sequences or "substantially identical derivatives, variants or equivalents" recited in the claims, the lack of direction/guidance presented in the specification regarding which structural features are required in order to retain functional activity of ecdysone receptor, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 79-81, 85 and 89-95 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to isolated nucleic acids encoding polypeptides consisting essentially of the amino acid of SEQ ID NO:10, nucleic acid molecules which consist

essentially of nucleotide sequence set forth in SEQ ID NO:9, isolated nucleic acids encoding polypeptides consisting essentially of the amino acid of SEQ ID NO:12 and isolated nucleic acids encoding polypeptides having substantial identity with SEQ ID NOs:10 and 12. The claims do not require that the polypeptides possess any particular conserved structure, or other disclosed distinguishing feature other than binding ecdysone.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of consisting essentially of or "substantial identity" to the specifically exemplified sequences and a requirement for binding ecdysone. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more that a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directe to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated nucleic acid molecules of comprising SEQ ID NOs:9 and 11, encoding for polypeptides of consisting of SEQ ID NOs:10 and 12, but not the full breadth of the claims meet the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 35 U.S.C. 112 is severable from its enablement provision (see page 115).

Claim 93 and 94 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated or cultured host cell comprising an expression vector, does not reasonably provide enablement for a host cell comprising an expression vector. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a broad genus of host cells comprising an expression vector which, in turn, comprises the claimed DNA. The specification contemplates three subgenera in which such host cells can be made and used. Specifically, the specification contemplates making and using the host cells in culture, in gene therapy, and in multicellular, transgenic organisms.

Case law directs that the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling). However, claims reading on significant numbers of inoperative

embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. *Ibid.*; *In re Cook*, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). Since the instant specification asserts that the claimed host cells can be made and used in three contexts, two of which are not enabled for the reasons set forth below, the instant fact pattern corresponds to the second situation wherein the claims encompass a significant number of inoperative embodiments and thus should be rejected under 35 U.S.C. § 112, first paragraph, as not being enabled for the full scope of the claims.

The specification asserts that host cells can be made and used in three contexts.

(1) The specification contemplates making and using isolated host cells in culture to produce the encoded protein recombinantly. Such is enabled, since the specification and prior art provide specific guidance on how to make and use host cells for this purpose. Undue experimentation would not have been required of the skilled artisan to make and use the claimed host cells in this context.

2) The specification also asserts that the claimed gene products can be expressed in transgenic animals and any technique known in the art may be used to introduce a transgene into animals to produce the founder lines of transgenic animals (page 41, lines 21-23). However, there are no methods or working examples disclosed in the instant application whereby a multicellular animal with the incorporated claimed gene is demonstrated to express the encoded peptide. There are also no methods or working examples in the specification indicating that a multicellular animal has the claimed gene "knocked out". The unpredictability of the art is *very high* with regards to making transgenic animals. For example, Wang et al. (1999. Nuc. Acids Res. 27: 4609-4618, pg 4617) surveyed gene expression in transgenic animals and found in each experimental animal with a single "knock-in" gene, multiple changes in genes and protein products, often many of which were unrelated to the original gene. Likewise, Kaufman et al. (1999. Blood 94: 3178-3184) found transgene expression levels in their transfected animals varied from "full" (9 %) to "intermediate" to "none" due to factors such as "vector poisoning" and spontaneous structural rearrangements (pg 3180, col 1,

2nd full paragraph; pg 3182-3183). Additionally, for example, the specification discloses that two possible techniques used to introduce the claimed transgene into animals include pronuclear microinjection and gene targeting in embryonic stem cells. However, the literature teaches that the production of transgenic animals by microinjection of embryos suffers from a number of limitations, such as the extremely low frequency of integration events and the random integration of the transgene into the genome which may disrupt or interfere with critical endogenous gene expression (Wigley et al., 1994 Reprod Fert Dev 6: 585-588). The inclusion of sequences that allow for homologous recombination between the transgenic vector and the host cell's genome does not overcome these problems, as homologous recombination events are even more rare than random events. Therefore, in view of the extremely low frequency of both targeted and non-targeted homologous recombination events in microinjected embryos, it would have required undue experimentation for the skilled artisan to have made any and all transgenic non-human animals according to the instant invention. Furthermore, regarding gene targeting in embryonic stem cells, the specification does not provide guidance for identifying and isolating embryonic stem cells or for identifying other embryonal cells which are capable of contributing to the germline of any animal. At the time of filing, Campbell et al. teaches that, "in species other than the mouse the isolation of ES cells has proved more difficult. There are reports of ES-like cell lines in a number of species...However, as yet there are not reports of any cell lines which contribute to the germ line in any species other than mouse" (1997. Campbell et al., Theriology 47(1): 63-72, see page 65, 2nd paragraph). Thus, based on the art recognized unpredictability of isolating and using embryonic stem cells or other embryonal cells from animals other than mice to produce transgenic animals, and in view of the lack of guidance provided by the specification for identifying and isolating embryonal cells which can contribute to the germ line of any non-human mammal other than the mouse, such as dogs or cows, the skilled artisan would not have had a reasonable expectation of success in generating any and all non-human transgenic animals using ES cell technology.

3) The specification also discloses that nucleotide constructs comprising the claimed gene can be used to genetically engineer host cells to express such products in vivo and that these products can be used in gene therapy approaches (page 35, lines 16-26). However, the specification does not teach any methods or working examples that indicate the claimed nucleic acid is introduced and expressed in a cell for therapeutic purposes. The disclosure in the specification is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. For example, the specification does not teach what type of vector would introduce the claimed nucleic acid into the cell or in what quantity and duration. Relevant literature teaches that since 1990, about 3500 patients have been treated via gene therapy and although some evidence of gene transfer has been seen, it has generally been inadequate for a meaningful clinical response (2001. Phillips, A., J Pharm Pharmacology 53: 1169-1174, abstract). Additionally, the major challenge to gene therapy is to deliver DNA to the target tissues and to transport it to the cell nucleus to enable the required protein to be expressed (Phillips, A.; pg 1170, ¶ 1). Phillips also states that the problem with gene therapy is two-fold: 1) a system must designed to deliver DNA to a specific target and to prevent degradation within the body, and 2) an expression system must be built into the DNA construct to allow the target cell to express the protein at therapeutic levels for the desired length of time (pg 1170, ¶ 1). Therefore, undue experimentation would be required of the skilled artisan to introduce and express the claimed nucleic acid into the cell of an organism to treat disease. Additionally, gene therapy is unpredictable and complex wherein one skilled in the art may not necessarily be able to introduce and express the claimed nucleic acid in the cell of an organism or be able to produce the encoded protein in that cell.

Due to the large quantity of experimentation necessary to generate a transgenic animal expressing the disclosed protein and to introduce and express the claimed nucleic acid in a cell of an organism for therapy, the lack of direction/guidance presented in the specification regarding how to introduce the claimed nucleic acid in the cell of an organism to be able produce the encoded protein, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art

which establishes the unpredictability of making transgenic animals and the unpredictability of transferring genes into an organism's cells, and the breadth of the claims which fail to recite any cell type limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Please note that the rejection of claims 93 and 94 could be overcome by amending the claims to recite, for example, "An isolated host cell..." because such an amendment would clarify that the claims are directed only to host cells which are to be made and used in culture as described in context 1) above.

Conclusions:

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shulamith H. Shafer, Ph.D. whose telephone number is 571-272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

SHS

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PRIMARY EXAMINER